REMARKS

Claims 1-28 have been canceled. Claims 29-52 have been added. Claims 29-52 are directed to prophylactic treatment of hemophilia with monomeric FIX and monomeric FIX compositions used for the prophylactic treatment of hemophilia.

Claims 29-46 supported

Claims 29-52 are specifically supported in the original application in paragraphs 21-24, 60-65, and 88-105, as well as original claims 1-28.

"Prophylactic" treatment and "sequestration" are specifically supported in paragraph 22, Example 3, Figure 6 and original claims 14-16.

Monomeric FIX preparation is specifically described in paragraphs 61, 64, and 65.

Properties of monomeric FIX are described in original claims 1-28, paragraph 60, and throughout the specification.

Sequestration of FIX not disclosed

The sequestration effect offered by monomeric FIX is an **unexpected result** obtained with the present invention. The pending claims recite the entirely unexpected result of being able to treat hemophilia "in advance" of a bleeding episode due to this surprising sequestration effect. None of the cited references describe sequestration of monomeric FIX.

Monomeric FIX not obvious

While native FIX may be monomeric *in vivo*, there is **no reason to expect** it to remain monomeric and active when formulated as a dry powder. Monomeric FIX is unique because FIX aggregates under high humidity conditions, when spray drying in the presence of ethanol, or when FIX is not prepared as described. Monomeric FIX has a mass median aerodynamic diameter (MMAD) of between 2 and 4 μm and has a fine particle fraction percent less than 3.3 μm (FPF %<3.3 μm) of at least 50%. This is required to maintain after-aerosolization activity/pre-aerosolization activity of at least 80% and achieve deep lung deposition of the

monomeric FIX. The deposition effect and subsequent sequestration of monomeric FIX for extended periods in the lungs is unique to monomeric FIX and has not been previously demonstrated. Thus a prophylactic treatment **could not** have been described or achieved without a monomeric FIX preparation.

Cited references not describe monomeric FIX

Lechuga-Ballesteros describes di- and tri-leucine preparations that may include FIX. They do not describe a prophylactic treatment with monomeric FIX, a composition comprising monomeric FIX, or the steps required to prepare monomeric FIX.

Lechuga-Ballesteros in light of Russell, Lechuga-Ballesteros in light of DeFrees, and Lechuga-Ballesteros in light of Platz do not provide a monomeric FIX, sequestration of monomeric FIX, or a prophylactic treatment with monomeric FIX. Thus the cited references do not provide **all of the elements** of the claimed invention.

CONCLUSION

The present invention provides a "needle-free" hemophilia treatment with an extended prophylactic effect. Compositions that maintain FIX activity during aerosol administration are required to achieve an effective treatment. The present invention achieves an FIX composition that is active *in vivo*, maintains activity after storage, and is effectively delivered to the deep lung tissue.

The Commissioner is hereby authorized to charge any fees which may be required, or credit any overpayment, to Deposit Account No. 50-3420(reference 31176282-004001 MDB).

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Respectfully submitted,

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